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Blood flow restricted exercise: providing more bang for buck in trained athletes?

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Blood flow restriction (BFR) has been utilised in physiology for centuries; from William Harvey's (1578-1657) initial use of a tourniquet to describe in detail the systemic circulation of blood, to the use in the last 40 years in the investigation of cardiovascular reflex responses, angiogenesis, skeletal muscle metabolism and fatigue. Recent investigation has largely focussed on the adaptive potential of BFR exercise training, with particular reference to skeletal muscle strength and hypertrophy and its use in the rehabilitation process. Others have continued to explore the potential for BFR in enhancing the skeletal muscle signalling response and subsequent improvement to whole body exercise performance. Adding to this latter aspect the paper by Christiansen et al [1] in this issue of *Acta Physiologica* provides further convincing evidence on the potential for BFR exercise to augment skeletal muscle signalling responses; particularly related to the physiological mechanisms associated with fatigue resistance and mitochondrial capacity.

In their study, recreational athletes (with a reasonable VO_{2max} of ~57 $ml.min^{-1}.kg^{-1}$) completed interval sessions consisting of three sets of three 2-minute running bouts. In an interesting experimental design these were performed alone, with BFR and under normobaric hypoxic conditions (F_IO_2 of 14%). By ensuring the level of skeletal muscle hypoxia (deoxygenation measured by NIRS) was consistent between the BFR and hypoxic conditions the investigators were able to ascertain whether hypoxia per se was involved in the adaptive process (as might be have been expected with the use of BFR). The exciting and novel observations were that BFR augmented the increase in mRNA expression of the Na^+,K^+-ATPase (NKA) complex ancillary protein phsopholemman-1 (FXYD1), which contributes to the maintenance of transmembrane Na^+ and K^+ ion gradients; critical in preserving skeletal muscle membrane excitability and thus contractile function [2]. They also demonstrated that BFR augmented the expression of specific isoforms of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), which is widely considered to be the key factor mediating exercise training-induced adaptations in mitochondrial capacity [3]. Interestingly, the augmented upregulation of these transcripts were unrelated to the severity of muscle hypoxia, lactate accumulation and activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMKII). Instead, the key physiological signals were related to the level of oxidative stress and fibre type specific 5' AMP-activated protein kinase (AMPK) signalling. This study clearly improves our understanding of the physiological stressors

involved in the regulation of NKA and PGC-1α expression, and how these stressors can be influenced by BFR. The study also adds support to the debate on the potential for BFR exercise interventions to have wider implications for performance, however there are a few important aspects that perhaps need to be considered.

The exercise was performed at a relatively moderate intensity of 105% of the individual lactate threshold, which was the highest tolerable intensity at which the exercise protocol could be completed alongside the selected magnitude of BFR and resulted in a rather modest 1.8-fold increase in total PGC-1α mRNA in the non-BFR control condition. As the authors acknowledge, this is much smaller than the changes observed after more intense or longer duration endurance-type exercise [4] as well as following sprint interval exercise [5]. As a consequence there would be a greater available capacity for further gene transcription. Indeed, Christiansen et al demonstrated that BFR augmented PGC-1α mRNA transcription up to 4.3-fold [1]. This is compared to the other studies that have investigated the effects of BFR on PGC-1α expression, in which there was either no effect [5] or an attenuated response [6]. In an alternative approach the study by Taylor et al [5] specifically chose sprint interval training with post-exercise BFR to ensure that a high training intensity was maintained, which is in line with current training theory [7]. This may have ultimately limited the available capacity for an augmented PGC-1α mRNA transcription in the BFR condition. Nevertheless, despite not observing enhanced PGC-1α mRNA expression, Taylor et al [5] did demonstrate augmented mRNA expression of other genes, specifically endothelial nitric oxide synthase (eNOS) and hypoxia-inducible factor-1α (HIF-1α), which play a key role in angiogenesis. Taken together, therefore, it seems that BFR exercise interventions have the capacity to augment the adaptive signalling responses across multiple physiological systems.

What makes the study by Christiansen et al [1] particularly timely is the general thought that phenotypic adaptations to exercise training are more difficult to elicit in well-trained athletes who already possess the necessary physiology to be competitive in their chosen event. Early research has highlighted the reduced plasticity of skeletal muscle in the trained state [8]. Moreover, this blunting of the adaptive scope in trained individuals, or in response to exercise training, is reflected at a molecular level [4, 9]. The "trained" status of participants in studies by Christiansen et al [1] (VO_{2max} of ~57 $ml.min^{-1}.kg^{-1}$) and Taylor et al [5] (VO_{2max} of ~60 $ml.min^{-1}.kg^{-1}$) suggest that, regardless of exercise intensity or modality, BFR may

overcome the blunted nature of the acute signalling response to exercise and act as a potent stimulus in enhancing a broad range of adaptive processes. Clearly, however, long term training studies are required to confirm whether these augmented signals translate into phenotypic changes. If this were to be the case improvements in physiological processes such as the muscle capacity for K^+ handling, oxidative ATP production [1], and morphological adaptations such as angiogenesis [5], brought about by BFR exercise training, would undoubtedly result in an enhanced performance capacity, particularly at high exercise intensities which are characterised by a non-steady-state, in which pulmonary (and muscle) VO_2, muscle metabolic milieu and acid-base balance all fail to stabilise and continue to increase/decrease until the limit of exercise tolerance, or task failure, occurs.

Considering that a key objective in elite training methods is to maximise the magnitude of event specific performance adaptation, BFR exercise may provide well-conditioned athletes with more 'bang for their buck' in augmenting the adaptive response to training. Anecdotally, such techniques are being explored by some elite performers, but the integration of BFR into training practice has yet to be fully achieved. This is understandable given the lack of clear evidence for performance enhancement, however the study by Christiansen et al [1] certainly adds to this initial body of literature. Hopefully, a greater understanding of the mechanisms and potential benefits of BFR exercise training might provide the impetus for the integration into training practice; although it is conceded that more information on the practicality, optimisation and safety of BFR exercise interventions is also required.

References

1. Christiansen D, Murphy RM, Bangsbo J, Stathis CG, Bishop DJ. Increased FXYD1 and PGC-1α mRNA after blood flow-restricted running is related to fibre type-specific AMPK signalling and oxidative stress in human muscle. *Acta Physiologica*.
2. McKenna MJ, Bangsbo J, Renaud J-M. Muscle K^+, Na^+, and Cl^- disturbances and Na+ ‐ K+ pump inactivation: implications for fatigue. *J Appl Physiol*. 2008; 104:288–295.

3. Olesen J, Kiilerich K, Pilegaard H. PGC-1alpha-mediated adaptations in skeletal muscle. *Pflugers Arch*. 2010; 460:153–162.
4. Perry CGR, Lally J, Holloway GP, Heigenhauser GJF, Bonen A, Spriet LL. Repeated transient mRNA bursts precede increases in transcriptional and mitochondrial proteins during training in human skeletal muscle. *J Physiol*. 2010; 23:4795–4810.
5. Taylor CW, Ingham SA, Ferguson RA. Acute and chronic effect of sprint interval training combined with post-exercise blood flow restriction in trained individuals. *Exp Physiol*. 2016; 101:143–154.
6. Conceição MS, Chacon-Mikahil MP, Telles GD, Libardi CA, Júnior EM, Vechin FC, DE Andrade AL, Gáspari AF, Brum PC, Cavaglieri CR, Serag S, Spiegelman BM, Hawley JA, Camera DM. Attenuated PGC-1α isoforms following endurance exercise with blood flow restriction. *Med Sci Sports Exerc*. 2016; 48:1699-1707.
7. Bangsbo J. Performance in sports - with specific emphasis on the effect of intensified training. *Scand J Med Sci Sports*. 2015; 25 Suppl 4:88-99.
8. Hoppeler H, Howald H, Conley K, Lindstedt SL, Claassen H, Vock P, Weibel ER. Endurance training in humans: aerobic capacity and structure of skeletal muscle. *J Appl Physiol*. 1985; 59:320–327.
9. Schmutz S, Däpp C, Wittwer M, Vogt M, Hoppeler H, Flück M. Endurance training modulates the muscular transcriptome response to acute exercise. *Pflugers Arch*. 2006; 451:678-687.